REMARKS

- Upon entry of this amendment, claims 1-23 and 29-33 will be pending.

The specification has been amended in order to comply with the requirements of 37 CFR § 1.821 through 1.825 for nucleotide and/or amino acid sequence disclosure. The amendments to the specification, as shown herein on page 2, are solely to address any informalities and do not introduce new matter. Applicants believe the amendments to the specification bring the application into compliance with the requirements for sequence disclosure, and as such, the objections to the specification should be withdrawn.

Claims 1 and 19 have been amended to clarify the cycle of therapy. Support for this amendment is found in the specification at page 7, lines 31-32 ("...period length of time for one treatment cycle is less than 14 days"). The amendments of Claims 12, 19, 29 and 30 have been made to clarify the term "reduced dose" and are supported by the specification at page 20, lines 4-9. Claims 4 and 5 have been amended to correct antecedent basis for the term "bcl-2 antisense oligonucleotide." Claims 16 and 31 have been amended to correct typographical errors in the sequence length (supported at page 11, lines 3-4 of the specification) and the description of the relationship between the mRNA and the bcl-2 gene (supported at page 2, lines 24-25 of the specification; it is well known that an mRNA does not "encode" a gene). Claims 20-23 have been amended to correct antecedent basis with respect to the term "chemoagent." Substantive amendments are discussed in more detail below.

THE REJECTIONS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH, SHOULD BE WITHDRAWN

The Examiner has rejected pending claims 12, 19, 29 and 30 under 35 U.S.C. § 112, second paragraph for failing to particularly point out and distinctly claim the subject matter which the Applicants regard as their invention.

Specifically, the Examiner contends that the specification as filed does not provide a standard for ascertaining a "reduced dose" (*See, e.g.*, the Office Action of March 18, 2003 at page 4, third paragraph).

Contrary to the Examiner's contention, Applicants respectfully point out that the specification clearly defines the term "reduced dose" as "a dose that is below the normally administered range, *i.e.* below the standard dose as suggested by the Physicians Desk

Reference, 54th Edition (2000), or a similar reference" (*See, e.g.*, page 7, lines 11-19 of the present specification). Moreover, the specification exemplifies the phase I trial of a bcl-2 antisense oligomer administered with two chemoagents at a reduced dose, *i.e.*, at "doses lower than the standard doses normally used for treatment of leukemia and other cancers" (*See, e.g.*, page 41, lines 9-11 at Example 3 of the present specification). Further, Applicants teach a reduced dose of a chemoagent used in conjunction with a bcl-2 antisense oligomer defined by objective comparative criteria, *i.e.*, as "a dose ..near or below the lower range of dosages when the chemoagent is administered without a bcl-2 antisense oligomer (page 20, lines 4-9 of the specification). It is well known in the art that the Physicians Desk Reference sets forth the "standard" doses of cancer therapeutics recognized as effective for cancer therapy. It is readily apparent to one skilled in the art that these standard doses represent what is typically effective without the use of Applicants' invention. While such standard doses of cancer therapeutics may be administered with Applicants' bcl-2 antisense oligonucleotide, doses of cancer therapeutics which are reduced compared to the recognized standard for efficacy are also unexpectedly effective (page 5, lines 5-8 of the specification). Therefore, one skilled in the art would be able to easily understand the claimed invention when reading the claims in light of the specification coupled with the teaching in the art.

The test for definiteness is whether those skilled in the art would be apprised of the scope of what is claimed (see M.P.E.P. 2173.02 citing *Solomon v. Kimberly-Clark Corp.*, 216 F.2d 1372, 1379, 55 USPQ2d 1279, 1283 (Fed. Cir. 2000); *In re Larsen*, No. 01-1092 (Fed. Cir. May 9, 2001) (unpublished)). Applicants assert that the claims as amended are clear to the skilled artisan, especially when taken in light of the specification and the level of knowledge in the field of cancer therapy. The specification, coupled with the knowledge in the art as of the effective filing date of the instant application provides one of skill in the art with ample guidance to determine the metes and bounds of the claims. Applicants believe that the scope of the subject matter embraced by the claims is clear.

THE REJECTIONS UNDER 35 U.S.C. § 102 SHOULD BE WITHDRAWN

The Examiner has rejected claims 1-5 and 13-18, relating to methods of treating or preventing cancer using a bcl-2 antisense oligonucleotide, under 35 U.S.C. § 102(b) as being anticipated by Webb *et al.* (1997) (Webb). The Examiner alleges that Webb encompasses a period of less than 14 days and thus anticipates the claimed invention.

Applicants submit that the Webb reference does not anticipate the claimed invention. Applicants respectfully point out that a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil of California*, 814 F.2d 628, 631 (Fed. Cir. 1987). Furthermore, "the identical invention must be shown in as complete detail as is contained in the ... claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236 (Fed. Cir. 1989). Applicants point out that Webb does not meet this standard, *i.e.*, Webb does not describe the treatment or prevention of cancer through the administration of a bcl-2 antisense oligomer for any period of time less than 14 days, and therefore does not anticipate the presently claimed invention in which bcl-2 antisense oligomer is administered in cycles of 2 to 13 days.

In Webb, therapy consists of a single two week course of treatment (*i.e.*, 14 days; *see* Webb's Methods at page 1138, column 1, lines 13-14). Thus, Applicants' one or more cycles of therapy, each lasting 2 to 13 days, is novel over Webb, because a cycle of therapy lasting 14 days cannot "encompass" a cycle of therapy lasting between 2 to 13 days, *i.e.*, they are mutually exclusive.

In rejecting the claims, the Examiner contends that Webb "evaluated the levels of bcl-2 measured by flow cytometry in lymph nodes of patient 6 during 7 and 14 days" and concludes that Webb therefore "encompasses a period less than 14 days..." (*see, e.g.*, the Office Action of March 18, 2003, page 5, fourth paragraph). Applicants submit that monitoring of bcl-2 levels during the treatment cycle at day 7, as described by Webb, is not equivalent to Applicants' treatment cycle lasting 2 to 13 days. It is clear from the entire reference, and in particular from the title of Fig. 2, that the monitored patient (patient 6) underwent treatment for the entire 2-week period and therefore that such monitoring does not represent a shortening of the treatment period set out in the Methods.

In view of the foregoing, Applicants respectfully request that the Examiner's rejection of claims 1-5 and 13-18 as anticipated by Webb be withdrawn.

THE REJECTIONS UNDER 35 U.S.C. § 103 SHOULD BE WITHDRAWN

The Examiner has rejected pending claims 1, 6-11 and 13-18 under 35 U.S.C. § 103(a) as being unpatentable over Webb in view of Jansen *et al.* (2000) (Jansen). The Examiner has also rejected pending claims 1, 6, 10, 12, 19 and 29-33 under 35 U.S.C. § 103(a) as being unpatentable over Webb and Jansen in further view of Klasa *et. al.* (2000) (Klasa). The Examiner contends that the claimed invention would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made.

The claimed invention relates to the use of bcl-2 antisense oligomers, administered at various doses to treat bcl-2 related disorders. In the present instance, the prior art cited by the Examiner does not render obvious the claimed invention, nor does it provide a reasonable expectation of success when using the treatment cycle of the duration of the claimed invention. The cited references do not provide a proper basis for an obviousness rejection under 35 U.S.C. § 103(a).

A finding of obviousness under 35 U.S.C. § 103(a) requires a determination of the scope and content of the prior art, the level of ordinary skill in the art, the differences between the claimed subject matter and the prior art, and whether the differences are such that the subject matter as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. *Graham v. Deere*, 383 U.S. 1 (1966). The proper inquiry is whether the art suggests the invention, and whether the art provides one of ordinary skill in the art with a reasonable expectation of success. *In re O'Farrell*, 853 F.2d 894, 903, 7 USPQ2d 1673 (Fed. Cir. 1988). Both the suggestion and the reasonable expectation of success must be founded in the prior art and not in the Applicants' disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

As illustrated above, Webb describes only a bcl-2 antisense oligomer therapy regimen that lasts for a period of 14 days. Jansen describes a clinical study in which a bcl-2 antisense oligonucleotide was administered at a dose of between 0.6-2.3 mg/kg/day, also for for 14 days, to patients with malignant melanoma, in combination with a standard dacarbazine regimen.

Webb and Jansen, taken alone or in combination, do not teach or suggest administering a bcl-2 antisense oligonucleotide in a treatment cycle consisting of less than 14 days (*i.e.*, 2 to 13 days as presently claimed). Notably, neither Webb nor Jansen, alone or in combination, provide one of skill in the art with a reasonable expectation of success using such a shortened treatment cycle. Moreover, Webb and Jansen, alone or in combination, do not provide one of skill in the art with the motivation to attempt the shortened treatment cycle of the claimed invention.

The Examiner contends that Webb and Jansen render the claims obvious in view of Klasa's alleged teaching that improved clinical outcomes could be achieved with standard or even lower doses of anticancer drugs when combined with antisense oligonucleotides. Klasa discloses a study in which SCID mice with B-cell lymphoma were given a bcl-2 antisense oligonucleotide at a dose of 5 mg/kg/day (or every other day) for 14 total doses. Klasa does not teach or suggest a treatment cycle of 2 to 13 days as presently claimed. Therefore,

neither Jansen nor Klasa overcomes the fundamental failure of Webb to teach or suggest a shortened bcl-2 antisense treatment cycle which is less than 14 days, nor do they provide the motivation necessary to try such a shortened treatment cycle. In the absence of the suggestion to treat with bcl-2 antisense for 2 to 13 days, the combination of Webb, Jansen and Klasa does not render the claimed invention obvious

Accordingly, Applicants submit that the rejection of claims 1, 6, 10, 12 and 29 to 33 for obviousness under 35 U.S.C. § 103(a) should be withdrawn.

Claims 19-23 are rejected as allegedly obvious by further combination of Webb, Jansen and Klasa with the teachings of Tortora, Adjei, Foran or Murren. Tortora is relied upon for its teaching of paclitaxel dosing at 20 mg/kg; Adjei is relied upon for its teaching of docetaxel at 60-100 mg/m^2, Foran is relied upon for its teaching of fludarabine at 25 mg/m^2 and Murren is relied upon for its teaching escalating doses of irinotecan starting at 50 mg/ m^2. None of these documents cure the failure of Webb to teach or suggest a bcl-2 antisense treatment cycle of 2-13 days. In addition, Tortora, Adjei, Foran and Murren teach only the standard efficacious doses of cancer therapeutics conventionally used prior to Applicants' invention. They are not below the the doses of cancer therapeutics administered without bcl-2 antisense oligomer as presently claimed. The total combination of references teaches only a 14-day treatment with bcl-2 antisense oligomer and the standard effective dose of a cancer therapeutic. Accordingly, Applicants submit that the rejection of claims 19-23 for obviousness under 35 U.S.C. § 103(a) should be withdrawn.

Furthermore, the non-obviousness of the present invention is supported by its unexpected properties, *i.e.*, the improved response in patients treated with a shortened bcl-2 antisense regimen administered over a period of 2 to 13 days and the success with lower than standard dose levels of chemoagents used in combination with such a bcl-2 antisense regimen (*In re Chupp*, 816 F.2d 643 (Fed. Cir. 1987)). For example, in patients treated by the claimed regimen, objective tumor responses and prolonged patient survival were noted, including patients with "treatment resistant cancer" who had experienced progressive disease during treatment with standard anticancer agents (*See* Example 1 of the specification, page 30, lines 15-30). Moreover, the response of patients to bcl-2 antisense oligomer administered for a short period of time demonstrated the unexpected efficacy and safety of the inventive therapy in the treatment of, *e.g.*, melanoma and prostate cancer (*See* Example 1, page 36, lines 1-7; Example 2, page 39, lines 6-15 and page 40, lines 5-12). Finally, better than expected responses were also observed using lower than standard dose levels of chemoagents when combined with a bcl-2 antisense regimen (*See* Example 3 of the specification; page 41, lines

6-13 and page 42, lines 9-12). Applicants have demonstrated numerous unexpected benefits of the claimed invention as compared to the cited art, and as such, the claimed invention is not obvious.

For all of the reasons above, Applicants respectfully submit that the rejections of the claimed invention under 35 U.S.C. 103(a) have been overcome, and respectfully request that the rejections be withdrawn.

CONCLUSION

Applicants respectfully request entry of the foregoing amendments and remarks into the file of the above-identified application. Applicants believe that each ground for rejection or objection has been overcome or obviated, and that all of the pending claims are in condition for allowance. Applicants also respectfully request consideration of the pending claims and withdrawal of the rejections. An early allowance is earnestly sought.

Respectfully submitted, by Jacqueline Bence
Reg No. 43,492

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Laura A. Coruzzi 30,742
Laura A. Coruzzi (Reg. No.)

PENNIE & EDMONDS LLP
1155 Ave. of the Americas
New York, NY 10036
(212) 790-9090